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February 11, 1992

VIA FAX

Paula Botstein, M.D.
Acting Director
Office of OTC Drugs
Food and Drug Administration
7520 Standish Place
Room 201
Rockville, MD 20855

RE: Docket No. 78N-0065

Dear Dr. Botstein:

On behalf of the NDMA Hydroquinone Task Group, I request a meeting with FDA to discuss our research program concerning hydroquinone. As you know, hydroquinone at the 2% level has had a long history of safe and effective use as a topical skin lightening agent in the United States and under the Tentative Final Monograph is classified as Category I, Generally Recognized as Safe and Effective. Nevertheless, in view of the recent NTP bioassay in which high doses of hydroquinone (HQ) were administered by gastric lavage, the NDMA task group is undertaking a comprehensive research project to evaluate the relevance, if any of the NTP findings to the topical application of 2% hydroquinone on human skin. Specifically, this research (described in some further detail below) will address the mechanisms of the renal tumorigenic effects reported in the oral NTP bioassay. This research effort is being undertaken in the context of other studies showing the lack of tumor-producing activity in, for example, Sprague-Dawley rats and the favorable toxicity profile of HQ following topical dermal application.

An in-depth review of the relevant available database on hydroquinone leads our task group to a conclusion that hydroquinone in OTC skin lightening preparations does not represent a human carcinogenic risk when used according to label directions. Nevertheless, since substantial time, effort and financial resources will be expended to further examine hydroquinone's safety profile in the context of the NTP study, NDMA believes that such a meeting with FDA is of key importance to the companies involved.

The NDMA task group concludes from the oral bioassays on hydroquinone, from additional as yet unpublished data on mechanisms of response, and from historical data on background tumors in the NTP series that: renal adenomas in male F-344 rats are

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associated with an interaction between nephrotoxicity and chronic nephropathy which may be unique to the male F-344 rat; renal adenomas in rats are associated with large oral exposures to HQ which are likely to overwhelm the normal metabolic pathways; mononuclear cell leukemia in female rats is not a reproducible effect indicative of carcinogenicity; the incidence of hepatocellular adenomas in B6C3F mice is well recognized as questionable evidence of carcinogenicity. In the additional context of the poor dermal absorption of HQ in OTC commercial preparations, the task group concludes that there is no relevant evidence to indicate that HQ represents a carcinogenic risk in humans when used according to OTC label directions on skin-lightening products.

Our research plans include, among other things, further development of the animal nephrotoxicity model to better understand the species differences in HQ metabolism and HQ-induced cell proliferation. Already this model has allowed the identification of an HQ metabolite that can induce nephrotoxicity in Sprague-Dawley rats. Additionally, with the low degree of penetration seen after HQ application to the skin and because clearance mechanisms rapidly remove HQ from the blood, the risks associated with dermal exposure to HQ should be extremely small even for the F-344 rat; nevertheless, the task group plans to implement a dermal bioassay -- the draft protocol for which we would like to share with FDA. The details of these research activities will be the subject of the meeting that we have requested.

Significantly in the context of the research we intend to undertake, the peer review comments of the NTP study on HQ concur with our conclusion that the NTP studies may not have direct relevance to dermally applied HQ. Both the principal and secondary reviewers of that study commented that a better rationale was needed as to why the oral route was chosen rather than the dermal route and that pharmacokinetic data should have been developed before the NTP study was undertaken. Indeed, one reviewer recommended that the report be deferred until the chemical disposition data could be incorporated into the peer review findings. We are hopeful that both the research that we have done to date as well as the research that we plan to develop will help answer the questions raised by the NTP study, which we believe are resolvable through an understanding of the mechanism of strain- and species-specific chemical-induced toxicity in the F-344 rat kidney.

In summary, based on the data available our working hypothesis as to how HQ exposure results in renal tumors in male F-344 rats is as follows. Following oral administration of HQ to rats, HQ is rapidly absorbed and rapidly metabolized in the liver to sulfate, glucuronide, and glucuronide conjugates. The glutathione conjugate and/or its metabolites

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are mildly toxic to the renal tubular epithelium which undergoes regenerative hyperplasia or cell proliferation. The susceptibility to nephrotoxicity can be transferred to Sprague-Dawley rats, which are normally not susceptible to this effect, by intravenous injection of the HQ-glutathione conjugate. The consequence of this stimulus to cell proliferation would be expected to result in an increased risk of tumorigenicity for male F-344 rats that would not be shared by other strains of rats or species of animals.

I look forward to your early response on this request for a meeting, which I reiterate is very important to our members. I will be in touch with you by telephone in the next day or so to review our request.

Sincerely yours,

R. William Soller, Ph.D.

R. William Soller, Ph.D.
Senior Vice President and
Director of Science & Technology

cc. W. Gilbertson, Pharm.D.

WS/kfm